REMARKS

Claims 1 – 9 and 12 - 19 are pending in the application. Claim 19 has been withdrawn on the basis it is directed to nonelected subject matter. Claims 1, 12 and 13 have been amended to correct obvious typographical errors. Therefore, the amendments do not add any new matter within the meaning of 35 U.S.C. §132. Entry of the amendments is respectfully requested.

1. Objection of Claim 1

Claim 1 is objected to on the basis the deletion of **0.5** was incorrectly identified with single brackets []. Applicants have amended the claims to correctly identify the amendment, and therefore reconsideration and withdrawal of this objection is respectfully requested.

2. Rejection of Claims 1 - 9 and 12 – 18 under 35 U.S.C. §103(a)

The obviousness rejection based on Ruchatz et al in EP 09 55063 ("Ruchatz") in view of Erni et al CH 663788 ("Erni") has been maintained with respect to claims 1 – 9 and 12 – 18.

Applicants traverse this rejection.

The Examiner suggests Ruchatz teaches an injectable formulation used to deliver anti-inflammatory agents, such as ibuprofen, which comprises a poloxamer and organic solvents. The Examiner also maintains that the only difference between Ruchatz and the instantly claimed subject matter is that Ruchatz does not disclose carprofen.

The Examiner turns to the disclosure by Erni of carprofen salts as useful in the preparation of analgesic pharmaceutical anti-inflammatory and antirheumatic compositions. The Examiner suggests it would be obvious for the skilled person to interchange the ibuprofen of Ruchatz with carprofen to arrive at the instantly claimed subject matter.

Applicant maintains Ruchatz does not disclose a composition which is a room temperature stable injectable solution, as herein required. Further, Ruchatz presents no teaching or guidance – evidentiary or otherwise that the compositions are room temperature stable or labile. Mere allegation that interchangeability is obvious is unsupported, because in the instant case the different properties – which are well appreciated in the art - of the ibuprofen of Ruchatz and the carprofen of Erni would not provoke one of skill in the art to use one of these NSAIDs for the other.

For example, carprofen is a weak acid, with a pKa of 4.3 and a high n-octanol/water partition coefficient of 41 at a pH of 7.4. In contrast, ibuprofen has a pKa of 4.43 and an n-octanol/water partition coefficient of 11.7 at a pH of 7.4. Both drugs possess anti-inflammatory, analgesic (peripheral and central sites of action) and anti-

pyretic properties. Both drugs act by decreasing the production of prostaglandins and thromboxane A2 from arachidonic acid released by damaged cell membranes. This is achieved by inhibition of the catalyst for the above reaction; cyclooxygenase (COX).

Ibuprofen is a non-COX-selective NSAID. Recent evidence suggests that additional anti-inflammatory properties are due to modulation of leucocyte activity, reduced cytokine production, inhibition of free radicals and signalling transduction. Ibuprofen may also exert a central analgesic action in the dorsal horn.

In contrast, carprofen is a COX-2 selective NSAID with a somewhat weak inhibition of COX isoenzymes. This property has helped it gain a licence for preoperative use because there is reduced risk of it affecting renal blooding flow during hypotensive episode under anaesthetic conditions.

Ibuprofen may be an effective analgesic in canines but there is evidence that it has a poor safety profile in canines with unacceptable risk of gastrointestinal ulceration and renal failure.

The attached study by Jackson, et al., entitled "Correlation of serum ibuprofen concentration with clinical signs of toxicity in three canine exposures" – Vet Hum Toxicol, 1991, Oct; 33(5): 486-8, assessed the correlation between serum ibuprofen concentration with clinical signs of toxicity in three canine exposures. No adverse clinical signs or abnormal laboratory parameters were observed when serum ibuprofen concentrations were less than 31 mg/ml. Melena and elevated blood urea nitrogen (azotaemia) were present in an animal with a serum ibuprofen of 138 mg/ml.

In a further study (attached) by Tsuchiya, et al., "Early pathophysiological features in canine renal papillary necrosis induced by nefiracetam" – Toxicol Pathol, 2005; 33(5): 561-9, investigated the early pathophysiological features in canine renal papillary necrosis (RPN) caused by nefiracetam in comparison to a control drug (ibuprofen at 50mg/kg/day for five weeks in beagle dogs). Ibuprofen displayed degeneration and necrosis in the renal papillary interstitium in week 5.

A case control study was performed using data from the National Animal Poison Control Center database with the aim of characterising the risk factors for gastro-intestinal ulceration and acute renal failure following ingestion of ibuprofen in the dog. Although the study failed to show a dose-response relationship, significant breed

differences in susceptibility to gastrointestinal ulceration was observed. German Shepards were found to be at particular risk for these adverse effects and required aggressive intervention even following ingestion of small amounts of ibuprofen. The time between ingestion to veterinary intervention was critical for both gastrointestinal and acute renal failure outcomes. See, Poortinga and Hungerford, "A case-control study of acute ibuprofen toxicity in dogs." – Prev Vet Med, 1998, May 1; 35(2): 115-24, attached.

Thus, Applicants submit that it is accepted in the art that drugs with significant efficacy and potency against COX-1 have greater potential to cause adverse effects particularly gastric ulceration.

The injectable aqueous compositions of the instant claims are for the provision of analgesia in small animals, especially companion animals, and in particular dogs. Thus, the skilled person when looking to provide a new injectable preparation comprising carprofen, which is to be used for the provision of analgesia in small animals, and in particular dogs, would not consider Ruchatz, which describes the use of ibuprofen, as **ibuprofen is toxic in dogs**.

As detailed above, ibuprofen and carprofen act very differently when used as a NSAID in formulations used in dogs. It would, therefore, not be obvious for the skilled person to interchange the ibuprofen of Ruchatz with carprofen to arrive at the instantly claimed subject matter.

Furthermore, if the ibuprofen used in the Examples of Ruchatz, were to be replaced with carprofen, the compositions provided would be unsuitable for administration by injection, and therefore, would fail according to the instantly claimed subject matter.

Applicants again direct the Examiner's attention to the examples of Ruchatz utilising carprofen instead of ibuprofen. The results are outlined below.

Ruchatz Example at paragraph [0024] utilises carprofen instead of ibuprofen:

Formula

Carprofen 5%
Propylene Glycol 20%
Copolymer A 22%
Copolymer B 5%
Purified Water q.s. 100%

Sodium chloride was not added, because it can cause an increase in viscosity. The product was already a semi paste/gel at room temperature with excessive foaming making it unsuitable for administration by injection. The carprofen was not completely dissolved in this formula.

Example 6 of Ruchatz et al was repeated utilising carprofen instead of ibuprofen:

Formula

Carprofen 1%
Propylene glycol 20%
Copolymer A 15
Copolymer B 10%
Purified Water q.s. 100%

Here, the carprofen was not in solution. The formulation foamed excessively when even briefly shaken. A gel like formula was obtained with air bubbles which were very difficult to dissipate. These characteristics of the formulation would make it unsuitable for administration by injection.

Carprofen is not compatible with the compositions of Ruchatz. Applicants again submit that this is due to the fact that ibuprofen and carprofen are very different chemical entities, and hence the skilled person would not expect that these entities can be interchanged without proper experimental evidence supporting the interchangeability. No such evidence has been provided, even in the light of the repeated presentation of evidence on non-interchangeability.

Finally, the compositions of Ruchatz are sol-gel compositions. As outlined in paragraph [0008] of Ruchatz, the compounds of Ruchatz can be administered at room temperature in liquid form intramuscularly and subcutaneously, and at body temperature they form a slow release gel, from which the active ingredients are released in a controlled way.

The compositions of the instantly claimed subject matter when administered subcutaneously have peak plasma levels of carprofen being achieved about 2.5 to 3.5 hours post administration, as shown in Table 1 of the application as filed. This is critical in so far as carprofen injectables are advocated for the control of post-operative pain. As discussed in the instant specification as filed, known injectable carprofen products on sale (Rimadyl® injectable, as disclosed in EP280887A) are suitable for intravenous

administration, see Figure 1 of the instant application for the pharmokinetic comparison. As detailed in the attached Rimadyl® injectable literature under the headings of "Indications" and "Dosage and Administration", Rimadyl® is indicated for the relief of pain and inflammation associated with osteoarthritis and for the control of postoperative pain associated with soft tissue and orthopaedic surgeries in dogs. For control of post-operative pain, Rimadyl® is administered approximately 2 hours before the procedure.

Thus, it is critical that the instant subject matter achieves circulating levels of carprofen quickly, and not as described in Ruchatz by way of a slow release gel. Such compositions, therefore, if given subcutaneously would not attain therapeutic levels in the time required for effective therapy.

It would, therefore, not be obvious for the skilled person to substitute carprofen into the compositions of Ruchatz to arrive at the presently claimed subject matter, as to do so would at best, if the carprofen was compatible with the compositions, result in a slow release of the drug from the site of inflammation and would not deliver the drug and the required therapeutic levels at the required time to have the required effect. If produced, the resulting formulations would, therefore, have no industrial application. As such, one of skill in the art would not, therefore, seek to deliver carprofen in parenteral form for canines for use as post operative pain relief via slow release delivery.

Accordingly, the Examiner is respectfully requested to reconsider and withdraw the outstanding.

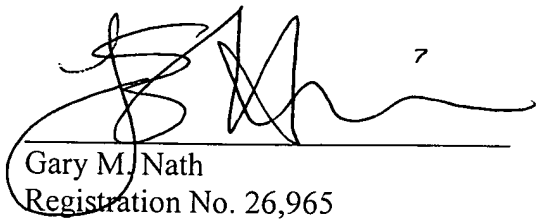
CONCLUSION

In light of the foregoing, Applicants submit that the application is in condition for allowance. Applicants respectfully request that the Examiner contact the undersigned attorney if it is believed that such contact will expedite the prosecution of the application.

In the event this paper is not timely filed, Applicants petition for an appropriate extension of time. Please charge any fee deficiency or credit any overpayment to Deposit Account No. 14-0112.

Respectfully submitted,

THE NATH LAW GROUP



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present subject matter.